The Provo Multicenter Early High-frequency Oscillatory Ventilation Trial: Improved Pulmonary and Clinical Outcome in Respiratory Distress Syndrome

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ABSTRACT. *Objective.* **To compare the hospital course and clinical outcome of preterm infants with respiratory distress syndrome treated with surfactant and managed with high-frequency oscillatory ventilation (HFOV) or conventional mechanical ventilation (CV) as their primary mode of ventilator support.**

Design. **A prospective randomized clinical trial.**

Setting. **Three community-based level III neonatal intensive care units.**

Subjects. **A total of 125 neonates who were 35 weeks or less estimated gestation requiring intubation and assisted ventilation for respiratory distress syndrome with arterial to alveolar oxygen ratio less than .50.**

Interventions. **Patients were randomized to continue CV (61 patients) or be changed to HFOV (64 patients) after exogenous surfactant administration (100 mg/kg). HFOV was used in a strategy to promote lung recruitment and maintain lung volume. Protocol respiratory care guidelines were followed; otherwise routine care was provided by each neonatal intensive care unit.**

Measurements and Main Results. **No differences were noted in demographic features between the two study groups. The study population birth weight was 1.51 ± .47 kg (mean ± SD), gestational age was 30.9 ± 2.5 weeks, and study entry age was 2 to 3 hours. Patients randomized to HFOV demonstrated the following significant findings compared with CV-treated patients: vasopressor support was less intensive; surfactant redosing was not as frequent; oxygenation improved more rapidly and remained higher during the first 7 days; fewer infants required prolonged supplemental oxygen or ventilator support; treatment failure was reduced; more patients survived without chronic lung disease at 30 days; need for continuous supplemental oxygen at discharge was less; frequency of necrotizing enterocolitis illness was lower; there were fewer abnormal hearing tests; and hospital costs were decreased. No differences were seen between the two study groups in the frequency or severity of patent ductus arteriosus, air leak, retinopathy of prematurity, or intraventricular hemorrhage. Length of hospital stay and survival to discharge were similar for HFOV- and CV-treated infants.**

Conclusions. **When used early with a lung recruitment strategy, HFOV after surfactant replacement resulted in clinical outcomes consistent with a reduction in both acute and chronic lung injury. Benefit was evident for preterm infants both less than or equal to 1 kg and more than 1 kg. In addition, early HFOV treatment may have had a more global effect on patient health throughout the hospitalization, resulting in reduced morbidity and decreased health care cost.** *Pediatrics* **1996;98:1044–1057;** ***ventilator, surfactant, high-frequency oscillatory ventilation, respiratory distress syndrome, premature infant, mechanical ventilation, continuous distending pressure, hospital cost, chronic lung disease, intraventricular hemorrhage, retinopathy of prematurity, necrotizing enterocolitis, brainstem audio-evoked response, oxygenation, neonatal morbidity, neonatal mortality.***

ABBREVIATIONS. RDS, respiratory distress syndrome; HFOV, high-frequency oscillatory ventilation; CV, conventional mechanical ventilation; IVH, intraventricular hemorrhage; CLD, chronic lung disease; HMD, hyaline membrane disease; NICU, neonatal intensive care unit; Pa/AO_2, arterial to alveolar oxygen ratio; $Paco_2$; partial pressure of carbon dioxide, arterial; PIP, peak inspiratory pressure; P_{aw}, mean airway pressure; PEEP, positive end expiratory pressure; IMV, intermittent mandatory ventilation; FIo_2, fraction of inspired oxygen; CDP, continuous distending pressure, ΔP, pressure amplitude; Pao_2, partial pressure of oxygen, arterial; PIo_2, partial pressure of inspired oxygen; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; PDA, patent ductus arteriosus.

In a previous single-center clinical trial involving premature infants with respiratory distress syndrome (RDS) before the availability of exogenous surfactant, Clark et al[1] demonstrated that high-frequency oscillatory ventilation (HFOV) started at a mean age of 9 hours and used for at least 72 hours reduced the severity and frequency of CLD at 30 days and 36 weeks postconceptional age when compared with infants managed with conventional mechanical ventilation (CV). The frequency of adverse clinical outcomes, such as intraventricular hemorrhage (IVH), was not increased in HFOV-treated patients. An earlier study, the multicenter HIFI trial,[2] showed no benefit from HFOV use in RDS for chronic lung disease (CLD) outcome at 28 days of age when HFOV was started at a mean age of 6 hours. Additionally, the HIFI study demonstrated statistically significant increases in IVH and certain types of airleak in HFOV-treated patients.[2] After these two presurfactant era studies published in 1989[2] and 1992[1], a third clinical trial has evaluated

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HFOV in preterm infants with RDS who were administered surfactant and randomized to HFOV or CV at 2 hours of age.[3] This 1993 Tokyo multicenter study by Ogawa and colleagues[3] did not show differences at 28 days of age in ventilator or oxygen use between HFOV- and CV-treated infants, however, only 75% of infants in both study groups received exogenous surfactant. The investigators did not identify any increase in intracranial morbidity or other adverse effects associated with HFOV use. To date, the three reports noted above are the only randomized clinical trials in which HFOV has been used relatively early in the treatment of RDS. Because the treatment strategies and study outcomes of these trials have not been strongly consistent, questions remain about efficacy and morbidity associated with HFOV as a primary treatment modality for RDS.

However, clear advantages for using early HFOV strategies in RDS have been reported in laboratory studies using preterm primate models of hyaline membrane disease (HMD). A reduction in pulmonary injury has been demonstrated in surfactant-deficient lungs when premature animals were ventilated immediately after delivery with HFOV.[4,5] These studies used a clinical HFOV strategy that promoted lung recruitment and maintenance of lung volume. More recent experiments by Jackson et al[6] have shown beneficial additive effects when this HFOV strategy was used early in HMD after exogenous surfactant. During HFOV in experimental RDS using nonprimate animal models, Froese et al[7,8] have shown beneficial effects of lung recruitment on pulmonary injury, lung inflation, and surfactant preservation. Combined, these animal studies suggest that an aggressive early approach to RDS that uses surfactant with an HFOV treatment strategy to optimize lung recruitment will reduce acute lung injury and should therefore improve pulmonary outcome.

Our purpose was to explore this experimental approach in the clinical setting, using HFOV after surfactant as a primary treatment modality for RDS. The study objectives were: (1) initiate HFOV within the first 2 hours of ventilator therapy, (2) administer exogenous surfactant to all patients as part of initial RDS treatment, (3) promote early lung recruitment, and (4) maintain lung volume. The hypothesis tested was whether maintaining adequate lung inflation after successful early lung recruitment with HFOV and surfactant would reduce pulmonary injury compared with CV and thus alter the clinical course and outcome of preterm infants with RDS. The primary outcome measured was CLD based on clinical parameters at 30 days of life and at discharge, including a CLD score, discharge oxygen use, and discharge inspired oxygen level.

Other issues of concern were secondary outcomes chosen to provide descriptors of the clinical course and to answer specific questions related to HFOV and the clinical study. Because randomization was planned shortly after delivery, the inclusion of potentially septic infants could have unduly biased one treatment group. A set of indicators of early infection were collected to evaluate for this potential bias. The laboratory finding that preterm primates treated with HFOV could undergo hepatic changes[9] has not been clinically evaluated. Data on hepatic function was therefore collected to help address this issue. Practical aspects of respiratory care, such as airway suctioning during HFOV, have also not previously been examined. We collected data on frequency of suctioning to detail this aspect of care. Other secondary outcomes chosen to describe the clinical course included fluid balance, vasopressor support, patent ductus arteriosis treatment, ventilation, oxygenation, acid/base balance, ventilator settings, ventilator use, oxygen use, air leak, treatment failure, suspected/treated necrotizing enterocolitis, retinopathy of prematurity, hearing screening, intracranial morbidity, disposition, discharge parameters, and hospital cost.

METHODS

Study Protocol

This study was designed as a multisite randomized noncrossover trial comparing the clinical course and outcomes of preterm infants with RDS requiring mechanical ventilation given surfactant and randomized to continued ventilator care with HFOV or CV. A detailed study protocol was used to provide uniformity of definitions and consistency in clinical decisions. Before the initiation of the clinical trial, the study protocol and consent form were reviewed and approved by the appropriate human subjects review committee at each study center.

Study Centers

Three level III community-based neonatal intensive care units (NICUs) participated in the study: (site 1) Utah Valley Regional Medical Center in Provo, UT, part of the not-for-profit Intermountain Health Care Corporation; (site 2) Memorial Hospital in Colorado Springs, CO, a nonprofit community hospital; and (site 3) Clinique Saint Vincent in Rocourt, Belgium, a not-for-profit private Catholic hospital operated by a congregation of Sisters of Saint Vincent de Paul. For the three sites the number of NICU admissions per year and the percent of outborn admissions were 500 and 15%, 450 and 45%, 600 and 30%, respectively.

Patient Eligibility

Patients were eligible for entrance into the study if they were younger than or 35-week estimated gestational age determined as the best available dating from serial fetal ultrasounds, mother's last menstrual period, and/or neonatal examination. Infants had to demonstrate respiratory distress at or shortly after delivery, clinically necessitating intubation and mechanical ventilation. An abnormal chest radiograph consistent with poor inflation and two arterial blood gases a minimum of 15 minutes apart were required to support a diagnosis of at least moderate respiratory insufficiency. Conventional ventilation parameters during a 2-hour stabilization period were also used as entrance criteria. These criteria included both indicators of poor oxygenation (arterial to alveolar oxygen ratio [Pa/AO_2] $<.50$) and poor ventilation (IMV >60/minutes, $Paco_2$ 45 Torr with peak inspiratory pressure (PIP) more than 16 cm H_2O for birth weight less than or equal to 1 kg, or PIP more than 22 cm H_2O for birth weight >1 kg). Patients more than 12 hours old and those with severe congenital defects or preexisting air leak were excluded. Infants with suspected or proven sepsis were not excluded. Informed consent was obtained from parents before participation of their infant in the study.

Randomization

A two-tiered balanced block design was used to reduce study bias from potentially complicated patient subgroups, eg, those infants of very low birth weight or those infants for whom randomization occurred late. The block design was thus based on birth weight ($\leq$1 kg, $>$1 kg) and age at randomization ($\leq$4 hours, $>$4 hours). Randomization was by blind card draw from separate sets of assignment cards for the four randomization categories. The goal for inborn patients was to obtain consent, establish entrance criteria, and complete randomization by 2 hours of age.

During this period infants experiencing respiratory distress were intubated and placed on CV for stabilization and further evaluation. If the infant met entrance criteria but was rapidly improving, randomization was not performed and the patient was not entered into the study. Only patients who continued to meet entrance criteria or who worsened and then met entrance criteria were given surfactant, randomized, and included in the study.

Surfactant

For the two United States locations (sites 1 and 2) the bovine-derived product, Survanta (Ross Laboratories, Columbus, OH) was used as the exogenous surfactant preparation. Because this product was not available in Europe during the study period, Alveofact, a bovine-derived surfactant, was used at site 3. Both surfactants were administered per manufacturer's recommendations: a dose of 100 mg/kg in aliquots with positioning. Redosing intervals were 6 to 12 hours with up to four doses allowed. Guidelines were established for redosing which required the patient to continue to meet study entrance oxygenation criteria ($Pa/AO_2 < .50$). Subsequent doses of exogenous surfactant were given only if the patient failed to improve to this level of oxygenation.

Ventilators and Strategies

For all patients during the 2-hour stabilization period, and for those patients randomized to CV, ventilation was provided by a time-cycled pressure limited neonatal ventilator (Sechrist, model IV-100B, Anaheim, CA). Synchronized neonatal ventilators and/or routine pulmonary function monitoring were not available at all study sites and were not included in the study protocol. Protocol parameters allowed adjustment of oxygenation by changes in inspired oxygen levels and by adjustment of mean airway pressure (P_{aw}) through changes in positive end expiratory pressure (PEEP) (3 to 7 cm H_2O) and PIP (30 cm H_2O for ≤1 kg, and 35 cm H_2O for >1 kg). Inspiratory times were kept between 0.35 to 0.55 seconds and reverse ratio inspiratory:expiratory times were not used. Ventilation was adjusted by increasing or decreasing PIP or by varying IMV. Ventilator rates more than 60/minutes were not used. The CV strategy was to increase PEEP as necessary to maintain end-expiratory volume and to increase PIP and IMV cautiously to provide adequate minute ventilation. CV was weaned by decreasing IMV and PIP for adequate or overventilation, and by weaning fraction of inspired oxygen (FIO_2) or then PEEP, for improving oxygenation.

HFOV was provided using the SensorMedics 3100 or 3100A device (SensorMedics Critical Care, Yorba Linda, CA). Inspiratory to expiratory time ratio was maintained at 0.33 and not changed. Ventilator frequency was set to 10 Hz, although in some very small infants this produced overventilation even at low power settings. In these small infants the oscillation frequency was increased to 15 Hz, which reduced tidal volume output and decreased overventilation. Oxygenation was controlled by changes in inspired oxygen levels and by adjustments of continuous distending pressure (CDP). Ventilation was controlled by adjusting the power output to increase or decrease ΔP. The HFOV strategy was to begin CDP at 1 to 2 cm H_2O above the P_{aw} used during the stabilization period on CV, and then further increase CDP in 1 cm H_2O increments if necessary until adequate lung recruitment was obtained. Adequate lung recruitment was evidenced by the ability to wean inspired oxygen, and by chest radiographs showing improved inflation (lung fields more radiolucent and diaphragm levels dropping to the eighth or ninth posterior rib). Lung inflation was considered optimum when the FIO_2 was able to be weaned to 0.30. After optimum lung volume was reached, CDP was slowly decreased in 0.5 to 1.0 cm H_2O increments as long as FIO_2 did not increase to more than 0.30. A decrease in CDP was also made for any chest radiograph that showed overinflation (marked radiolucency, depressed diaphragms, and/or pleural bulging between rib interspaces). Ventilation was controlled by adjusting ΔP to normalize $PaCO_2$. Pressure amplitude was weaned in response to improving ventilation, seen as decreasing $PaCO_2$ values without changes in ΔP. Infants were then either extubated to hood oxygen or transitioned on CV and then weaned to extubation, depending on whether they exhibited active respiratory effort, or were prone to apnea or decreased respiratory drive while on HFOV.

For both ventilators target PaO_2 values were 55 to 75 Torr and target $PaCO_2$ values were 35 to 45 Torr. Permissive hypercapnia ($PaCO_2$ >50 Torr) using reduced ventilator settings was not used. Arterial blood gases were obtained at least every 2 hours until stable and then every 4 to 6 hours. Chest radiographs were obtained at least every 12 hours or as clinically indicated. Transcutaneous PO_2, PCO_2, and pulse oximetry were used on all infants as blood gas trend indicators.

Treatment Failure

The following treatment failure criteria were modeled on those used previously in the study of Clark et al.[1] A patient was considered to fail ventilator support if PaO_2 less than 50 Torr for more than 2 hours despite $FIO_2 = 1.0$ and increases in P_{aw} or CDP; $PaCO_2$ more than 60 Torr for more than 2 hours despite adjustments to improve ventilation; there was clinical evidence of cardiac dysfunction at ventilator settings required to maintain adequate gas exchange; there was development of air leaks that destabilized the patient on the current ventilator; or the patient required hand ventilation to establish adequate gas exchange. Patients randomized to HFOV could also fail treatment if CDP more than 20 cm H_2O for more than 2 hours for infants less than or equal to 1 kg or more than 25 cm H_2O for infants more than 1 kg. Patients randomized to CV could fail treatment if IMV more than 60/minutes; PIP more than 30 cm H_2O or PEEP more than 6 for infants less than or equal to 1 kg; or, PIP more than 35 cm H_2O or PEEP more than 8 for infants more than 1 kg. At the point of treatment failure the patient was released from randomization assignment and the decision to change or continue with the current ventilator was left to the best clinical judgment of the investigator. The study was therefore a noncrossover design. Data compilation was continued on patients meeting treatment failure criteria. All patients were analyzed with their initial randomization group.

Data and Analysis

The data set was predefined as part of the clinical trial protocol. Initial data were collected at the time of randomization and included data on patient demographics, entrance criteria, randomization, and early treatment time points. Qualifying blood gas values were also included. The next data collection was completed at discharge and provided summary information concerning the clinical course and hospitalization. In addition, all arterial blood gases with associated ventilator parameters were obtained and analyzed. At site 1 data on cost of care were abstracted from case-mix computerized records after study closure and a blinded analysis was performed. These true cost data included room, equipment, supplies, nursing, laboratory studies, radiographic studies, pharmacy, physician, and other professional support. All data were entered into a database for subsequent analysis using personal computer statistical packages (NCSS v6.0, Kaysville, UT or StatXact-Turbo, Cambridge, MA).

Data variables were tested for normality and most were found to be nonnormal. Data that were normally distributed are represented as mean ± SD. Otherwise, the central tendency is shown as the median and its 95% confidence limits [median (5, 95% confidence limits [CL])]. Statistical analyses were performed using exact nonparametric tests for two sample populations or for 2 × n contingency tables, or if tests between means were appropriate, the two sample t test was used. For the arterial blood gas and ventilator parameters comparison a repeated measures analysis of variance approach was used. Fisher's least significance difference test was applied for post hoc analysis at specific time points. Because the arterial blood gases were not obtained at scheduled times, all arterial blood gases for each patient were used. If more than one set of blood gas values or ventilator parameters were available in a time interval, then these values were averaged for that patient to develop a single value. The following intervals were used from the time of study start: −4 hours to 0 hours labeled as 0 hours; 0 to 2 hours labeled as 1 hours; 4 ± 2 hours intervals from 4 hours to 24 hours; then 8 ± 3 hours intervals to 48 hours; then 12 ± 4 hours increments to 7 days.

Evaluation of factors that may have had confounding effects on pulmonary outcome was performed using multiple logistic regression analysis. Birth weight and ventilator treatment group were included in all analyses as independent factors. The effect of prenatal steroid administration, treatment site, surfactant type, and PDA were then tested on two pulmonary outcome variables: CLD score more than 0 at 30 days and oxygen need at discharge where PIO_2 more than 160 mm Hg (see below). The number of patients included in the analysis of each outcome parameter var-

ied depending on whether the infant survived or whether finalized data were available if the infant was transferred to another facility. Outcome data are complete for all survivors discharged to home. Statistical significance was evaluated at the $P = .05$ level for all tests. Data are grouped as demographic parameters, and as pulmonary, clinical, and hospital outcomes.

Altitude Considerations

Sites 1 and 2 are located in the Rocky Mountains at elevations of 1388 meters (4553 feet) and 1831 meters (6008 feet), respectively, and site 3 is near sea level at 150 meters (492 feet). Oxygen needs at altitude based on inspired oxygen levels not only reflect deficits secondary to lung disease, but can also reflect compensation for decreases in P_{IO_2} due to lower atmospheric pressure. A patient with decreased pulmonary reserve may have adequate P_{aO_2} at sea level where P_{IO_2} = 160 Torr, but exhibit hypoxemia at altitude where P_{IO_2} may be much less. Similarly, babies who require supplemental oxygen at discharge from high altitude nurseries may have normal saturations off oxygen if taken to lower altitude. Because of these differences, direct comparisons of patients' oxygen needs among nurseries at different altitudes may be misleading. In this study these data have been normalized to sea-level values.

Study Closure

This trial was designed before the commercial availability of exogenous surfactant and was implemented in the first year of widespread surfactant use. The initial study design was for three treatment arms: HFOV-alone, surfactant+HFOV, and surfactant+CV. In estimating a sample size based on CLD as the primary treatment outcome, no information was available at the time that gave a good estimate of the effect that surfactant+HFOV might have on pulmonary outcome. Data on the frequency of CLD at 28 days of life in surfactant+CV-treated patients, about 20%,[10] was substituted as a best guess. Using an α value of 0.05 at a power of 0.80, a sample size of 300 patients was calculated for the three group study (PASS, NCSS, Kaysville, UT) based on a reduction in CLD frequency similar to that seen in the HFOV-alone trial of Clark et al[1] that was about 10%. A safety analysis and reevaluation of sample size was scheduled after 50 patients had entered the study and was performed by the authors at 18 months into the trial. These preliminary results were published in abstract form.[11] From the safety analysis three findings were evident: (1) early HFOV use appeared as safe as CV, (2) HFOV-alone was no more efficacious than surfactant+CV, and (3) the decrease in frequency of CLD in the surfactant+HFOV group was greater than estimated in the best guess. Enrollment into the HFOV-alone group was closed, the study sample size was recalculated based on only two treatment groups, and the new estimate of effect was derived from the safety analysis. In this estimate a more stringent statistical boundary was set by increasing the power requirement from 0.80 to 0.90. This yielded a final sample size of 120 to 130 patients. The trial was terminated after 37 months when 125 patients were enrolled.

RESULTS

Enrollment

At site 1 patient enrollment occurred from November 1991 through January 1995 with informed consent obtained from 127 patients. The majority of consents was acquired prenatally for high risk mothers 35 weeks gestation or less when preterm delivery appeared imminent. Eighty-three of the 127 patients met study entrance criteria and were randomized. For comparison this represented 37% of the 223 infants of less than or 35 week gestation who were intubated and mechanically ventilated for more than 24 hours during this period. Of the other 140 potential study patients, 29 were more than 12 hours of age on admission and did not meet entrance criteria, 30 were outborn and consent was not possible, 71 were not enrolled because consent could not be obtained, and in at least 10 infants, the parents did not wish to consent. There were no significant differences in birth weight distribution or in mortality outcome between qualifying study and nonstudy patients. At site 2 active enrollment occurred between April 1992 and June 1994 with 13 patients being studied. Site 3 actively enrolled patients from November 1993 to June 1994. During this period the nursery had 399 admissions, 148 of which were of less than or 35 weeks gestation. Sixty patients were mechanically ventilated and 35 met study entrance criteria. Informed consent was obtained for 29 infants.

Overall, 66.4%, 10.4%, and 23.2% of patients were enrolled from sites 1 to 3, respectively, for a total of 125 study patients. There were 21 infants less than or equal to 1 kg (16.8%) and 104 patients more than 1 kg (83.2%). There were 100 infants enrolled before they were 4 hours old (80%) and there were 25 infants (20%) enrolled when they were 4 to 12 hours old. A total of 64 patients was randomized to HFOV and 61 patients to CV. The χ^2 analysis of the balanced block categories indicated even randomization distribution ($P = .8401$). The distribution of patients by site into HFOV and CV study groups was also unbiased (χ^2, $P = .9746$).

TABLE 1. Demographic Data

	HFOV Group	CV Group
No. of patients	64	61
No. of patients ≤1 kg	11	10
Birth weight (kg)	1.56±0.46	1.46±0.47
Best gestational age (wks)	30.8± 2.2	30.1± 2.7
Male	68.8% (44/64)	54.1% (33/61)
Outborn	23.6% (15/64)	14.8% (9/61)
Prenatal steroid use	29.7% (19/64)	18.0% (11/61)
Cesarean section	62.5% (40/64)	65.5% (40/61)
1-min Apgar score	7 (5, 7)	6 (5, 7)
5-min Apgar score	8 (8, 9)	8.5 (8, 9)
Age on admission (min)	14 (12, 17)	12 (9, 15)
Age at intubation (min)	12 (6, 30)	18 (6, 54)
Age at randomization (h)	2.9 (2.4, 3.3)	2.0 (1.4, 3.0)
$P_{a/A}O_2$ 0–2 h of age	0.25 (0.20, 0.29)	0.21 (0.18, 0.27)
Age at first surfactant dose (h)	3.4 (2.7, 3.7)	2.3 (1.9, 3.3)

Patient Demographics

Characteristics of the two study groups are shown in Table 1. Average birth weights were 1.45 to 1.55 kg and estimated gestational ages were 30 to 31 wk. Most infants were male, inborn, delivered by cesarean section and did not receive prenatal steroids. The majority of patients was intubated and admitted to the NICU by 20 minutes of age. Median age at randomization was 2 to 3 h of life with surfactant administration occurring 20 to 30 minutes after randomization. The median Pa/AO_2 values (0.21 to 0.25) during the stabilization period indicated moderate to severe RDS in both groups. There were no statistically significant differences in any of the demographic parameters for patients randomized to HFOV or CV.

Pulmonary Outcomes

Suctioning Frequency

The number of times per day that patients underwent airway suctioning was tabulated. Differences were found on days 1 to 3 where CV patients were suctioned more frequently than were those that were HFOV ventilated ($P < .05$), ie, two to three times per day vs four to six times per day. By day 4 both groups were suctioned five to six times per day.

Surfactant Dosing

Based on a redosing criteria of Pa/AO_2 less than .50, patients were given subsequent doses of surfactant if oxygenation did not improve. The number of patients receiving one, two, three, or four doses of surfactant is seen in Fig 1. The percentage of patients receiving more than one dose of surfactant was lower in the HFOV-treated group, 15.6% (10/64) vs 45.9% (28/61) for the CV group ($P < .001$, odds ratio 4.58). In addition, the median number of doses was less for HFOV-ventilated patients ($P < .001$).

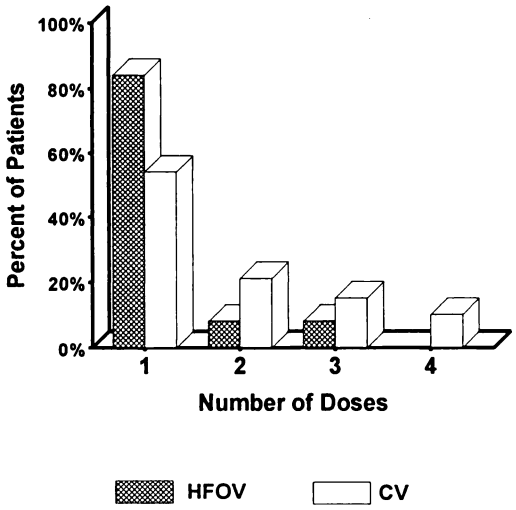

Fig 1. Surfactant dosing. HFOV, hatched bars; CV, open bars. The percent of patients in each study group that received one, two, three, or four doses of surfactant is shown. Both the median number of doses and the fraction of patients that received more than one dose of surfactant were higher in the CV-treated group than in the HFOV-treated group, 46% for CV vs 16% for HFOV ($P < .001$). The total number of surfactant doses was 28% less in the HFOV group, 79 vs 110. Redosing was based on failure to achieve Pa/AO_2 0.50 after the previous surfactant dose.

Air Leak

The number of patients that developed pneumothoraces and/or pulmonary interstitial emphysema was not significantly different between study groups (Table 2).

Oxygenation

Arterial Pao_2 values were well controlled in each study group to 65 ± 16 Torr and did not vary between groups over the 7 days for which blood gas data were analyzed. Fig 2 shows data on P_{aw} (CDP), FIO_2, and Pa/AO_2. HFOV CDP was greater than CV P_{aw} over the first week of life ($P < .001$). From 1 to 16 hours individual time point differences were evident, with HFOV CDP being about 2 cm H_2O higher than CV P_{aw} ($P < .05$ each time point). Inspired oxygen levels were weaned more rapidly with HFOV, usually to less than 0.30 by 8 hours of age. During the first 48 hours of life FIO_2 was lower in HFOV patients compared with CV patients ($P < .05$ each time point). In the HFOV group, Pa/AO_2 rapidly increased and exceeded 0.50 by 4 hours into the study. From 4 to 36 hours HFOV Pa/AO_2 remained higher than for CV ($P < .05$ each time point). Similarly, during the first 7 days of treatment there were strong main effects with respect to FIO_2 requirements and oxygenation (Pa/AO_2), showing improvements for the HFOV study group compared with CV ($P < .001$ each).

Ventilation

The degree of ventilation support for HFOV- and CV-treated patients during the first week is shown in Fig 3. Arterial Pco_2 values were kept within protocol guidelines of 35 to 45 Torr. Improving ventilation was seen in both groups during the first 12 hours as evidenced by decreasing $Paco_2$ with the appropriate response of decreasing ΔP for patients on HFOV and decreasing IMV for patients on CV. Thereafter HFOV ventilation support remained relatively constant (ΔP = 17 to 19 cm H_2O), but CV ventilation support continued to be weaned. By 6 days the mean IMV rate had dropped from 24/minute to 12/minute.

Acid/Base Status

There were no differences in acid/base status between the two study groups during the first 7 days of study. Both groups demonstrated the development of mild hyperventilation, increasing pH (7.32 to 7.36) and decreasing $Paco_2$ (42 to 37 Torr) values over the first 12 hours as ventilator adjustments were made and the condition of the infants stabilized. After 24 hours $Paco_2$ values were 40 to 44 Torr, slowly increasing with a coincident slow increase in serum bicarbonate levels. The pH remained relatively constant at 7.31 to 7.33, with a mild combined respiratory and metabolic acidosis.

Oxygen Use

Median days of oxygen administration for infants less than or equal to 1 kg was not significantly dif-

TABLE 2. Pulmonary Outcomes

		HFOV Group	CV Group
Airleak	PIE or pneumothorax	12.5% (8/64)	18.0% (11/61)
Treatment failure	Infants meeting criteria	1.6% (1/64)*	14.8% (9/61)
CLD/survival at 30 d of age	Score 0	49	34
	Score 1	6	14
	Score 2	5	6
	Score 3	2	3
	Score 4	2	2
	Died	0	2
	Median rank test	HFOV < CV†	
	Survival without CLD	76.4% (49/64)†	55.7% (34/61)
Oxygen use	≤1 kg: days on O_2	60.6 (25.5, 96.8)	98.8 (40.4, 154.0)
	(no. on O_2 > CV median)	18.2% (2/11)†	71.4% (5/7)
	>1 kg: days on O_2	13.2 (6.6, 24.3)†	27.6 (14.3, 37.7)
	(no. on O_2 > CV median)	28.3% (13/46)†	50.0% (24/48)
Ventilator use	≤1 kg: Days on HFOV	5.3 (1.6, 9.8)	10.2 (0, 17.8)
	Days on CV	15.2 (1.0, 56.1)	44.5 (11.3, 103.0)
	Total days MV	24.7 (3.7, 61.4)	53.7 (28.4, 103.0)
	No. on MV > 28 d	45.9% (5/11)*	100% (7/7)
	>1 kg: Days on HFOV	2.1 (1.2, 4.0)	0
	Days on CV	0.2 (0.1, 1.0)	4.2 (2.8, 5.6)
	Total days MV	4.1 (1.7, 6.0)	4.5 (3.0, 6.1)
O_2 use at discharge	Patients on continuous flow O_2	33.3% (17/63)*	49.2% (27/59)
Discharge P_iO_2	All (mm Hg)	136 (135, 151)‡	155 (135, 158)
	≤1 kg (mm Hg)	136 (128, 159)*	157 (135, 180)
	>1 kg (mm Hg)	137 (135, 159)	153 (135, 160)

* $P < .01$.
† $P < .05$.
‡ $P < .06$; values are mean ± SD or median (5, 95% confidence limits).

ferent between the HFOV and CV treatment groups (Table 2). However, for infants more than 1 kg median oxygen use was significantly less for HFOV compared with CV ($P = .043$). The percent of infants requiring prolonged oxygen use (longer than the median duration of use of oxygen for CV-treated patients) was significantly less for those patients initially randomized to HFOV (≤1 kg: $P = .049$, odds ratio 11.25; >1 kg: $P = .037$, odds ratio 2.54).

Ventilator Use

Ventilator data for infants less than or equal to 1 kg and more than 1 kg are shown in Table 2. Although there was no difference noted between groups in median total days, the number of infants less than or equal to 1 kg on ventilator support for more than 28 days was less for those in the HFOV group ($P = .038$).

Treatment Failure

The number of patients who met treatment failure criteria are detailed in Table 2. Sixty percent of patients meeting criteria were more than 1 kg. Treatment failure occurred within the first 12 hours in 70% of the infants, and none after 36 hours. Patients who failed their assigned ventilator usually met more than one criterion. The number of patients meeting criteria who were randomized to CV was higher than for those randomized to HFOV ($P = .008$, odds ratio 10.90).

CLD

A scaled score, similar to the one used by Clark et al,[1] was used to grade the level of ventilator and oxygen support at 30 days. The CLD score was graded 0 to 3 based on sea-level equivalent inspired oxygen ranges of 0.21, 0.22 to 0.30, 0.31 to 0.40, and more than 0.40, respectively. The score was increased by one if the infant remained intubated with IMV more than 10/minutes or P_{aw} more than 8 cm H_2O. Table 2 shows the CLD score data. Survival without oxygen or ventilator requirement at 30 days was more frequent in the HFOV-treated patients ($P = .015$, odds ratio 2.59). The degree of CLD was also less as evidenced by a lower median CLD score for the HFOV group ($P = .021$).

Discharge Oxygen Use

The need for oxygen at discharge was assessed based on the amount of nasal cannula oxygen flow required to maintain transcutaneous saturation levels at 90 to 95%. A partial pressure of inspired oxygen (PIO_2) was also determined based on ambient oxygen levels; calculated from FIO_2 measured while the infant was in hood oxygen or estimated from an in-house validated nomogram using nasal cannula oxygen flow, respiratory rate, and infant's current weight as parameters. Oxygen use at discharge is shown in Table 2 along with median PIO_2 values. There were fewer HFOV than CV patients on continuous oxygen at discharge ($P = .039$, odds ratio 2.57). Even with the frequent need for additional oxygen, median PIO_2 did not exceed sea-level ambient oxygen (160 mm Hg) for either group. Median PIO_2 levels at discharge were actually less than sea-level ambient for all HFOV patients ($P < .001$). For infants less than or equal to 1 kg, PIO_2 levels in HFOV-treated patients were lower than PIO_2 for CV-

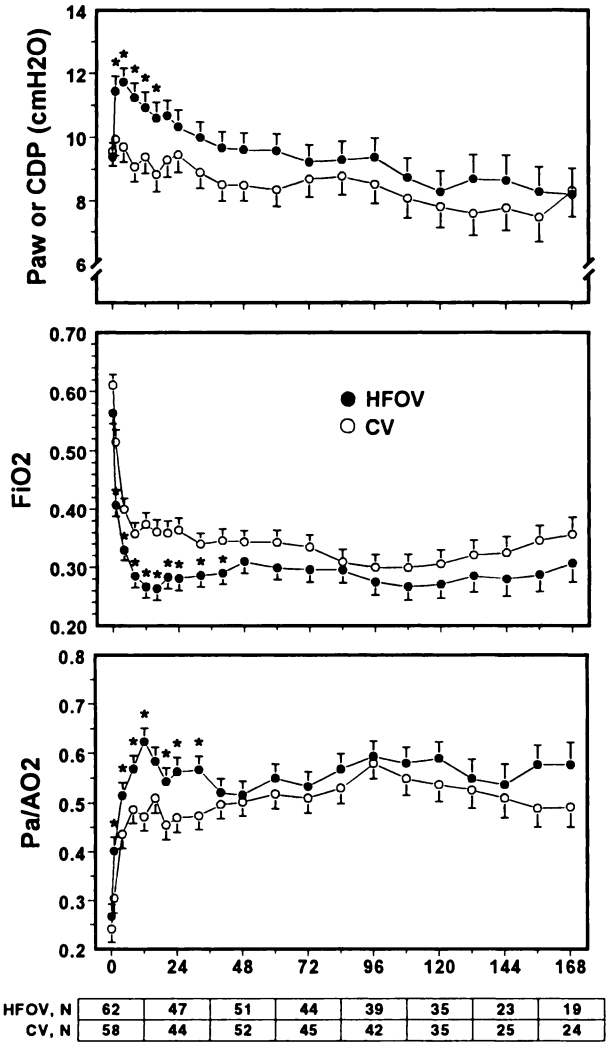

Fig 2. Oxygenation parameters. HFOV, filled circle; CV, open circle. The values shown are mean ± SD. Top panel, P_{aw} and CDP (cm H_2O). Over the first 7 days of treatment HFOV CDP was higher than CV P_{aw} ($P < .001$). In *post hoc* analysis, HFOV CDP was significantly higher (about 2 cm H_2O) at timepoints from 1 to 16 hours compared with CV P_{aw} ($P < .05$). Middle panel, FIO_2, fractional inspired oxygen. FIO_2 decreased rapidly in HFOV-treated patients, reaching <.30 by 8 hours of age and remaining lower than for CV patients over the first 7 days ($P < .001$). *Post hoc* analysis illustrated time point differences at 1 to 40 hours during the study ($P < .05$). Bottom panel, Pa/AO_2, arterial to alveolar oxygen ratio. Pa/AO_2 was higher in HFOV-treated neonates by 1 hours. Individual time point differences were noted from 1 to 32 hours ($P < .05$). HFOV Pa/AO_2 remained higher than CV Pa/AO_2 over the first 7 days ($P < .001$).

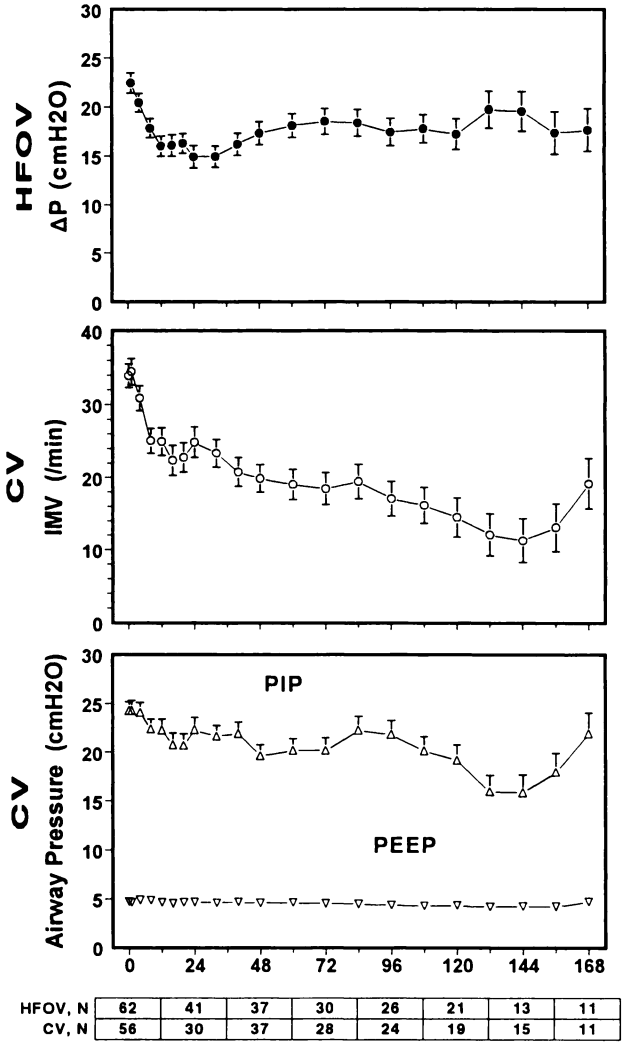

Fig 3. Ventilator parameters. HFOV, filled circle; CV, open circle, open triangles. The values shown are mean ± SD. Top panel, ΔP, HFOV pressure amplitude (cm H_2O). Mean HFOV ventilation pressures decreased over the first 24 to 36 hours from 23 cm H_2O to 15 cm H_2O. For the rest of the initial week of treatment average ΔP ranged between 17 to 19 cm H_2O. Middle panel, IMV, CV intermittent mandatory ventilation rate (per minute). Mean IMV rates decreased during the first 24 hours from 35 per minute to 23 per minute. A gradual decrease in IMV was seen during the rest of the first week of treatment. IMV had decrease to 12 per minute by 6 days. Bottom panel, PIP, CV peak inspiratory pressure and PEEP, positive end expiratory pressure (cm H_2O). PIP levels were relatively constant during the initial 5 to 6 days of treatment, with changes in CV ventilation occurring through decreases in IMV (see middle panel). PEEP was held constant at 5 cm H_2O throughout the first 7 days.

treated patients ($P = .018$) and nearly so for all HFOV patients ($P = .056$).

Clinical Outcomes

General

As indicators of possible infection that may mimic RDS, total white blood cell count, immature to total neutrophil count ratio, and platelet count, were recorded on admission and at 24 hours. There were no significant differences between groups in these early infection indicators and all values were within normal ranges. Cultures of blood on admission and endotracheal secretions before surfactant replacement were also evaluated and no differences were found between groups in the frequency of positive cultures. Liver function was assessed by determination of transaminase and bilirubin levels at the start of the first and second weeks of life. Values were within normal ranges and no differences were found between study groups at either time point. To evaluate hydration and volume resuscitation status, daily total fluid intake and urine flow were measured during the first 7 days. A fluid balance ratio

(24 × urine flow/total fluid intake) was calculated to correct urine output for variations in fluid administration. Fluid intake began at approximately 110 mL/kg/day on day 1 and gradually increased to about 140 mL/kg/day by day 7. There were no statistically significant differences between groups for total fluid intake either over the 7-day period or on any given day. Similarly, the fluid balance ratio was equivalent between groups, with both HFOV- and CV-treated patients demonstrating a diuresis on the second and third days of life. Urine flow was lowest (~2 mL/kg/hour) during the first 24 hours of life ($P < .05$); reached highest levels (5 to 6 mL/kg/hour) on days 2 to 3 of life ($P < .05$); then stabilized at 4 to 5 mL/kg/hour for days 4 to 7 of life.

Vasopressor Support

Study protocol did not specify criteria for use of dopamine or dobutamine, but most investigators began vasopressor support after blood volume resuscitation if a patient continued to exhibit hypotension, poor perfusion, or if there was poor myocardial function seen on echocardiography. Because the duration and number of agents used were indicative of the degree of support required, the hours of use of all agents were summed to represent an index of vasopressor support. The percent of patients treated in each study group was the same, about 42 to 43% (Table 3), however, the number of patients who required vasopressor support and had a high use index (>120 hours) was fewer in the HFOV-ventilated group ($P = .035$, odds ratio 4.22).

PDA Management

PDA was diagnosed by echocardiographic evaluation with moderate to severely sick infants receiving serial examinations during the first week of life. The decision on what constituted a symptomatic left-to-right ductal shunt, and the timing and type of PDA treatment was left to the investigator. No difference was noted in the frequency of treated PDA between study groups (Table 3).

Suspected/Treated NEC

Patients were evaluated throughout their hospitalizations for clinical changes consistent with necrotizing enterocolitis (NEC) or NEC-like illness. Each infant was categorized as normal—no clinical disease or workup; suspected—significant feeding intolerance and abdominal symptoms requiring a septic workup, antibiotics, and interruption of feedings for more than 24 hours, but no radiographic evidence of pneumotosis intestinalis; NEC responding to medical treatment—abdominal symptoms and radiographic pneumotosis intestinalis but managed without surgery; NEC requiring surgical treatment—surgical intervention for significant bowel pathology. The number of patients with suspected/treated NEC (Table 3) was less in the HFOV treatment group compared with the CV treatment group ($P = .032$, odds ratio 3.67).

Hearing Screening

Brainstem audio-evoked response was used before discharge to evaluate an infant's auditory system

TABLE 3. Clinical Outcomes

		HFOV Group	CV Group
Vasopressor support	Patients on vasopressors	42.2% (27/64)	42.6% (26/61)
	Use index >120 h	16.6% (4/27)*	42.3% (11/26)
PDA	Treated PDA	45.4% (20/44)	40.4% (19/47)
NEC illness	No symptoms	60	49
	Suspected	2	9
	Medically treated	2	2
	Surgically treated	0	1
	Suspected or treated	6.2% (4/64)*	19.7% (12/61)
Retinopathy	No eye exam	17	16
	No ROP	35	32
	Stage 1 ROP	6	3
	Stage 2 ROP	3	3
	Stage 3 ROP	2	6
	≥Stage 3 + ROP	1	1
	Any grade ROP	25.6% (12/47)	28.9% (13/45)
	ROP > stage 2	6.4% (3/47)	15.6% (7/45)
Intracranial morbidity	No craniosonography	8	6
	Normal exams	41	36
	Grade 1 IVH	8	8
	Grade 2 IVH	1	2
	Grade 3 IVH	2	1
	Grade 4 IVH	0	5
	Periventricular leukomalacia (PVL) (with/without IVH)	4	3
	Abnormal study	26.8% (15/56)	32.7% (18/55)
	Grade 3–4 IVH or PVL	10.7% (6/56)	16.4% (9/55)
Hearing screen	Abnormal brainstem audio-evoked response	1.9% (1/52)†	16.0% (8/50)

* $P < .05$.
† $P < .01$; values are mean ± SD or median (5, 95% confidence limits).

function. Infants who met criteria for hearing screening in premature infants were evaluated. There were fewer abnormal brainstem audio-evoked response results (Table 3) in the HFOV treatment group than in the CV treatment group ($P = .015$, odds ratio 9.71). There were six mild and three severely abnormal tests that were a combination of peripheral and central conduction defects.

Retinopathy of Prematurity (ROP)

All infants who met criteria for ROP screening underwent serial ophthalmologic evaluations. The maximum extent of retinopathy for each patient and the frequency of occurrence of abnormal findings are shown in Table 3. There was no difference in the number of infants who developed retinopathy or in the severity of ROP disease between the two study groups. One infant in each group advanced to threshold disease (stage 3+) and was surgically treated.

Intracranial Morbidity

As a minimum, craniosonography was performed for high-risk infants on day 3 and 7 of life to assess for the occurrence of IVH. Other studies were done in the second to third week of life and/or before discharge to evaluate for periventricular leukomalacia. Grading of IVH was done using the scale of Papile et al.[12] The highest grade of IVH and/or the presence of periventricular leukomalacia for study patients are shown in Table 3. The overall frequency of abnormal craniosonographic studies and the incidence of severe intracranial morbidity were the same for the two study groups.

Mortality

All HFOV-treated infants survived. In the CV study group two infants less than or equal to 1 kg died. One death occurred at 15 d secondary to candida sepsis, and one infant died at 14 hours of age from severe hypoxia and metabolic acidosis. There was no difference in mortality between the study groups.

Hospital Outcomes

Table 4 shows the patient disposition categories. Of all study patients 89% were discharged directly home at the end of their hospitalization. No statistically significant differences were noted between groups in disposition, or in weight, age, or gestation at discharge. Total hospital costs were determined for the 83 study patients at site 1 (Table 4). Median hospital costs were less if patients were randomized to HFOV (Fig 4). This was true for infants less than or equal to 1 kg ($P = .044$) and >1 kg ($P = .030$).

Analysis of Confounding Factors

Potential confounding factors were evaluated for their effect on the CLD score at 30 days and on the need for supplemental oxygen at discharge. A logistic regression model was used with CLD score more than 0 and P_{IO_2} at discharge more than 160 Torr as outcomes, while birth weight, ventilator treatment group, and the parameter of interest were used as independent factors. In general, birth weight and ventilator group were significant factors in prediction models for CLD at 30 days, $P < .001$ and $P < .040$, respectively. Neither birth weight nor ventilator treatment group were significant factors in the model prediction of oxygen need at discharge. Prenatal steroid treatment, hospital study site, surfactant type, and presence or treatment of PDA were all tested as parameters of interest. None contributed significantly in model predictions of CLD or discharge oxygen need. In this patient population these factors did not appear to exert strong independent effects on CLD outcome parameters.

DISCUSSION

The results of this controlled trial in premature infants with RDS clearly indicate a beneficial role for the early use of an aggressive HFOV lung recruitment strategy after surfactant therapy. Despite the fact that this study was designed to include a wider cross-section of infants with RDS than in previous studies, allowing the larger (up to 35 weeks gestation age) and not quite as sick infant (Pa/AO_2 0.25 to 0.50) to participate without the requirement to meet rescue or ventilator failure criteria, multiple areas could be identified where significant improvements in outcome existed for both smaller (≤1 kg) and larger infants (>1 kg) solely on the basis of initiating pulmonary care with an HFOV treatment strategy. Using this approach no increase in morbidity was found for patients treated with HFOV. Specifics of these and other findings are discussed below.

TABLE 4. Hospital Outcomes

		HFOV Group	CV Group
Disposition of survivors	Discharged home	56	55
	Transferred	7	4
	Not discharged	1	0
At discharge	Hospital days	44.0 (30.6, 52.6)	46.9 (39.2, 56.0)
	PCA (wks)	37.1 (36.5, 37.9)	37.5 (36.6, 38.0)
	Weight (kg)	2.30 (2.13, 2.52)	2.30 (2.17, 2.47)
Hospital cost*	≤1 kg (×$1000)	N = 9	N = 7
		103.2 (52.0, 162.5)†	192.5 (61.5, 262.0)
	>1 kg (×$1000)	N = 33	N = 34
		32.2 (25.2, 39.3)†	45.6 (37.7, 671)

* For patients at site 1 only; values are median (5, 95% confidence limits).
† $P < .05$.

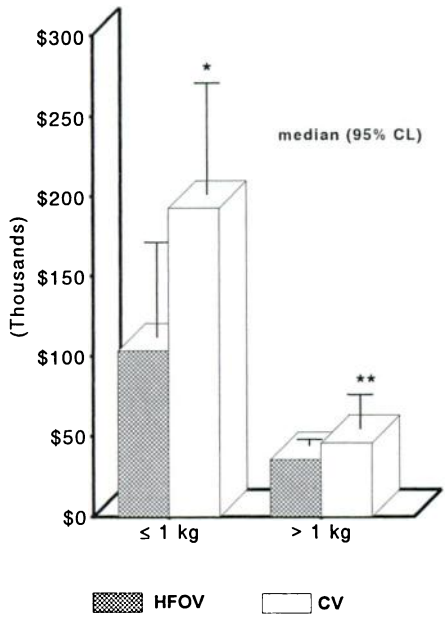

Fig 4. Hospital cost. HFOV, filled bar; CV, open bar. The values shown are median and 95% confidence limits. Illustrated are total hospital cost information for the 83 patients at site 1. Lower total health care costs were seen in HFOV-treated patients, both less than or equal to 1 kg (*P = .044) and >1 kg (**P = .030).

Study-related Issues

Although not excluded in the HIFI trial[2] or in the study of Ogawa et al,[3] potentially infected infants were not included in the study of Clark et al[1] because of difficulty in discriminating between RDS caused from lung immaturity or due to infection. In addition, there has been general concern that septic infants are more difficult to stabilize during initiation of HFOV and that sepsis could therefore be a cause for HFOV treatment failure. Because of the early enrollment nature of the current trial, infants with presumed or actual sepsis were not excluded. To clarify this problem data were collected to evaluate for indicators of early infection in both culture-negative and culture-positive infants. There was no evidence in complete blood count indices or culture results to suggest that infection was an issue in using HFOV, or that either group was more affected by early infection.

One issue not previously addressed in HFOV clinical studies is the finding of a correlation between HFOV and the development of hepatic lesions in a preterm primate model of HMD.[9] The lesions were characterized by severe fatty change and/or cytoplasmic vacuolization and edema. Data on hepatic function were collected in our study patients during the first and second weeks of HFOV treatment. There was no detrimental effect of HFOV on hepatic function as might have been seen by elevated liver enzymes or impaired bilirubin processing. In the clinical setting, biochemical liver dysfunction secondary to HFOV treatment did not occur.

Several reports suggest an association between NICU fluid management practices and the development of bronchopulmonary dysplasia.[13–15] No differences were noted between the two study groups in the amount of fluids they received or in their fluid balance. Fluid management factors that previously have been noted to increase the risk of CLD did not appear to create a bias for the development of CLD in our study population. Also in contrast to previous reports,[14,15] regression modeling of our study did not find that the presence or treatment of patent ductus arteriosus (PDA) was a factor influencing the occurrence of CLD.

Pulmonary Outcomes

During development of the HFOV strategy used in this trial there was concern that endotracheal tube suctioning would negate the CDP lung recruitment effect during the acute phase of RDS. Another concern was the standard practice of disconnecting the ventilator circuit to perform suctioning, which interrupts CDP and could also contribute to lung volume loss. Study guidelines were thus written to discouraged routine suctioning (every 4 hours) for HFOV patients during the first 48 hours. Suctioning for clinical indications (eg, visible secretions in the endotracheal tube, increasing $Paco_2$ values, loss of chest wall vibration) was allowed. As a result, HFOV patients were suctioned less frequently early in the study. Although no untoward effects were seen in HFOV patients who did not have this initial routine suctioning, it is interesting to speculate whether the increased number of suctioning episodes in CV patients might have contributed to their higher CLD scores. Whether episodic suctioning can actually cause or worsen lung injury is not clear. There is some evidence to suggest that in a laboratory setting lung rerecruitment can be adequately achieved after disconnect on HFOV,[16] and that in-line suction catheters can preserve airway pressure better and with less change in oxygenation.[17,18] However, the question concerning the best approach to airway secretion management for patients on HFOV both early and later in the ventilatory course remains to be answered.

Based on the criterion of continuing to manifest poor oxygenation, CV patients were given significantly more doses of exogenous surfactant than were patients treated with HFOV. A reduction of need for exogenous surfactant in HFOV-treated compared with CV-treated patients has been reported in a retrospective analysis of one center's experience.[19] The combination of a single dose of exogenous surfactant and HFOV has been shown to reduce pulmonary injury in a primate model of HMD,[6] and this may be sufficient to alter the need for subsequent doses of exogenous surfactant. A decrease in the degree of early lung injury should both promote the health of type II surfactant-producing pneumocytes and reduce the amount of surfactant inactivation from capillary protein leak. These effects may limit the requirement for further surfactant administration. Additionally, the continuous maintenance of lung recruitment with HFOV using CDP markedly diminishes tidal volume cycling of the lung and thus may decrease the need for properties that surface active materials confer.

Although both study groups had significant intrapulmonary shunts before randomization as mea-

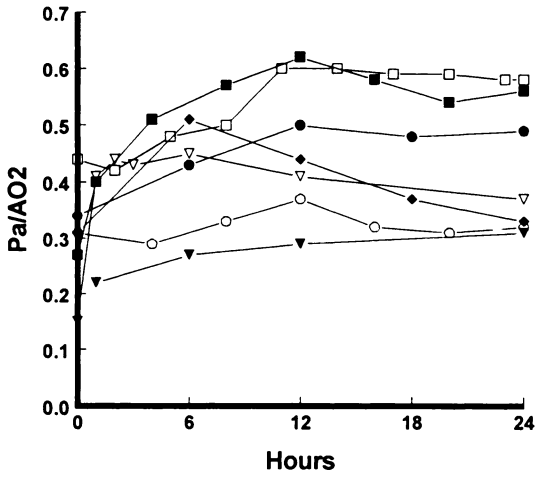

Fig 5. Recent HFOV and surfactant studies. Open box, HFOV in primate HMD model;[5] open triangle, single dose bovine surfactant TA;[27] filled diamond, single dose bovine surfactant;[28] filled triangle, multiple dose human surfactant[29] open circle, presurfactant HFOV clinical trial;[1] filled circle, Tokyo surfactant + HFOV clinical trial;[3] filled box, current study with surfactant + HFOV. Pa/AO_2 data from the current and six recently published studies using surfactant + HFOV, HFOV, or surfactant + CV illustrate oxygenation differences during the first 24 hours of treatment. Although patient populations differ to some degree, Pa/AO_2 should be a relatively independent indicator of lung recruitment in an uninjured preterm lung. Our study most closely approximates the results of the Meredith et al[5] nonsurfactant HFOV study in a primate model of HMD.

sured by Pa/AO_2 less than 0.25, rapid improvement in oxygenation was seen in those patients treated with HFOV. Inspired oxygen levels decreased and Pa/AO_2 increased in response to maintaining HFOV CDP higher than CV P_{aw}. Oxygenation with HFOV remained higher than with CV over the first week of life. Oxygenation and the lung recruitment strategy used in this trial are closely tied. Although lung volumes were not measured in this study, previous studies have shown a relatively linear relationship between CDP and lung inflation during HFOV.[20,21] The increase in Pa/AO_2 and reduction in FIO_2 seen in HFOV-treated patients is consistent with choosing a CDP operating point higher than the lung opening pressure. This allows the lung to recruit and lung volume, lung surface area, and oxygenation to increase. The degree of lung inflation required to achieve this level of oxygenation improvement is probably at or above normal functional residual capacity.[21] The oxygenation response seen in this study was similar to that seen in the Tokyo study,[3] where Pa/AO_2 increased more rapidly in the HFOV treatment group and reached 0.50 by 12 hours of age. For comparison, oxygenation response in terms of Pa/AO_2 changes during the first 24 hours of life are shown in Fig 5 for the Tokyo study and five other surfactant and/or HFOV studies where data have been published. The surfactant studies shown are those where early single dose therapy was used with CV, except for the human surfactant study where only multiple dose data were available. Overall, the oxygenation improvement seen in our study most closely resembles the response seen by Meredith et al[5] in preterm primates with HMD not treated with exogenous surfactant. We speculate that this finding is most likely related to the use of similar HFOV lung recruitment strategies.

Mean $Paco_2$ values were normal and within study target range for both groups during the first week of treatment. Ventilation support for HFOV, ΔP, remained relatively constant during this time, but minute ventilation support for CV decreased through small decrements in PIP, and through consistent weaning of IMV. Although spontaneous respiratory rate was not recorded in the study data set, the inability to wean ΔP in HFOV patients may relate to a suppression of spontaneous breathing by this mode of ventilation, a phenomena that has been previously noted.[22,23] The degree of spontaneous breathing while on HFOV may have significant implications for weaning, not only from the standpoint of establishing adequate spontaneous minute ventilation, but also from the standpoint of adequate endogenous surfactant release which is dependent on tidal volume breathing.[24]

Median days of oxygen administration and the frequency of prolonged oxygen use were less in those patients randomized to HFOV with birth weight more than 1 kg. HFOV-treated infants less than or equal to 1 kg were also noted to have a decreased frequency of long-term oxygen use. For infants more than 1 kg, median total ventilator days indicated short treatment courses for both study groups, about 4.0 to 4.5 days. However, fewer HFOV infants less than or equal to 1 kg were on prolonged ventilator support (>28 days). Similar trends were seen in the study of Clark et al,[1] where median total ventilator time was 14 to 16 days for HFOV-treated patients and 30.5 days for those treated with CV.[1] In general, HFOV patients in our study appeared to have less oxygen and ventilator exposure than did patients treated with CV. Not all patients were able to be extubated directly from HFOV, and as a result, transition periods on CV were required. For the larger infants (>1 kg) these periods were short (<24 h), but for small infants (≤1 kg) the median transition time on CV was 15 days. Clinical parameters that would define the appropriate time to wean from HFOV or transition to CV have not been fully developed. Weaning to CV after 72 hours of HFOV was not as effective as remaining on HFOV for a median duration of 7 days when this issue was examined in the trial of Clark et al[1]. The median duration of HFOV in our study was 5.3 days for less than or equal to 1 kg and 2.1 days for more than 1 kg. The decrease in median HFOV use days between our study and that of Clark et al[1] may relate to the improvement in lung function and decrease in lung injury afforded by the addition of exogenous surfactant to the treatment protocol.

Although our trial was not designed as a crossover study, many infants who failed CV were changed to HFOV for rescue. As a result, median days on HFOV for patients less than or equal to 1 kg who started on CV were higher than median HFOV days for patients started on HFOV. Failure on CV may obligate the infants to a longer treatment course compared with having begun on HFOV initially. In

this study the frequency of treatment failure was significantly higher for CV than for HFOV. A similar pattern was noted in the San Antonio study, where cross-over from CV to HFOV was also more frequent ($P < .01$).[1] The opposite was true for the HIFI trial were significantly more HFOV patients failed and met cross-over criteria to CV ($P < .01$).[2] Although somewhat different failure criteria were used in the various studies, one aspect of airway pressure management strategy may be critical. The current, San Antonio,[1] and Tokyo[3] studies all used starting HFOV CDP higher than the CV P_{aw} used before randomization. In the HIFI trial, FIO_2 was increased in response to hypoxia and HFOV CDP was the same as CV P_{aw}.[2] This latter approach may have delayed placing the HFOV CDP operating point above lung opening pressure, causing the lung to persist in a partially deflated state. Inability to recruit the lung late in the course in the HIFI trial was evident when P_{aw} treatment failure criteria of 15 cm H_2O was met when the infants were 6 days of age.[2]

The degree and incidence of oxygen and ventilator need in survivors as measured by the CLD score at 30 days was significantly less for patients initially treated with HFOV compared with those randomized to CV. Except for birth weight and ventilator treatment group, no other factors in the current data, such as prenatal steroid use, surfactant type, PDA, or study site, exhibited significant effects on CLD outcome. As another indicator of CLD, the need for supplemental oxygen at discharge was compared between study groups. In relation to CV-treated patients, fewer HFOV patients were discharged on continuous supplemental oxygen. Although a large number of patients in both groups needed oxygen at discharge to maintain normal transcutaneous saturation values, the primary reason was a decreased ambient PIO_2 at sites 1 and 2 because of their location and altitude. Even with the supplemental oxygen, the median PIO_2 for both groups was less than sea level ambient, and the median PIO_2 for HFOV patients was lower than for those treated with CV. In fact, the PIO_2 at discharge in HFOV patients was 15% below sea-level ambient. Discharge at altitude offers a natural hypoxia challenge for patients with borderline pulmonary reserve. The ability of the HFOV patients to tolerate a below sea-level ambient PIO_2 suggests less residual lung injury or shunt component compared with the CV-treated patients. Although not previously described as an indicator of CLD, discharge PIO_2 in this HFOV patient population is consistent with an improved degree of pulmonary recovery. The lack of the same degree of pulmonary reserve in the CV-treated patients is worrisome. These patients would generally not require extra oxygen at sea-level and their lack of reserve could be silent until challenged. It is not known whether this lack of reserve in our CV survivors with mild CLD can be translated into the alveolarization failure recently reported by Coalson et al[25] in nonsymptomatic primate bronchopulmonary dysplasia survivors. However, the speculation that permanent alveolar loss can silently accompany this clinically mild degree of chronic lung injury is a concern for the future pulmonary health of these patients. Early HFOV treatment during the acute phase of RDS appears to decrease the degree of chronic lung injury which is represented by a loss of oxygenation reserve at discharge.

Clinical Outcomes

The fact that fewer neonates treated with HFOV had a high vasopressor use index, and that fluid resuscitation (total fluid intake) during the first 48 hours on HFOV was not more than for patients in the CV group were both somewhat surprising results. In using a lung recruitment strategy with HFOV, mean lung volume should be higher than with CV at equivalent P_{aw}. An increase in mean lung inflation will act to reduce average right atrial volume. Consequently, one might expect decreased cardiac output and the need for increased vasopressor support, or a need to increase right-sided preload pressure with fluid resuscitation so that flow is maintained. This was seen in the HIFI trial where volume expansion need and vasopressor use were higher in the HFOV treatment group ($P = .09$ and .01, respectively).[2] However, in our study the same number of patients in each group were placed on vasopressors and there was no difference between groups in total fluid intake. With the HFOV strategy used in this trial, cardiovascular instability did not appear to be a significant clinical problem. This is in agreement with work by Kinsella et al[26] that demonstrated no adverse effect of HFOV on cardiac output in an HMD primate model when HFOV CDP was equal to CV P_{aw} at levels that did not cause lung overinflation. HFOV patients in our study seemed to improve their cardiovascular status more rapidly, as evidenced by fewer HFOV than CV patients requiring prolonged vasopressor use.

Patients in the HFOV study group were noted to have suspected/treated NEC and abnormal hearing screening tests less frequently compared with patients in the CV treatment group. The clinical significance of this difference as it relates to ventilator randomization is unclear. Because the occurrence of these abnormalities may be related to ischemia, one could speculate that the rapid sustained improvement in oxygenation and the less prolonged need for vasopressor support could have decreased the risk for these gastrointestinal and neuroauditory injuries. No differences existed between HFOV and CV groups regarding the frequency/severity of ROP or IVH, and there was no difference in mortality at discharge.

Hospital Outcomes

Despite reductions in oxygen and ventilator use, improvements in CLD, and decreases in prematurity-associated morbidity, no reduction was seen in length of hospital stay for HFOV-treated patients compared with CV-treated patients. Median postconceptional age at discharge was 37 weeks. It would appear that with current RDS treatment strategies, nursery factors other than pulmonary care, such as those associated with discharge planning, nipple feeding training, family education, and devel-

opmental care are now dictating readiness and timing for discharge. This is a positive effect, because pulmonary morbidity from RDS now appears to play much less of a role late in the hospital course. In some communities home-care-based early discharge programs are available and influence discharge timing, but these types of programs were not available at the three study sites.

Total care costs were available for analysis from study site 1. At this facility cost for NICU service areas, ie, nursing, respiratory therapy, neonatology, and patient space, was based on in-hospital developed patient acuity scales, so the median total cost was strongly influenced by the average level of care given during the hospitalization. Significant differences in median costs between HFOV- and CV-treated patients for infants less than or equal to 1 kg and more than 1 kg are consistent with HFOV patients needing lower degrees of support, exhibiting stability earlier in the hospital course, and having fewer critical setbacks.

Study Limitations

Our results must be interpreted in context. The patient populations served by the three study sites do not represent diverse ethnic, cultural, or socioeconomic groups, but rather almost solely consist of upper-middle class families. Mothers were in good health, had access to and participated in prenatal care, and were well nourished. There were very few small-for-date infants. Extrapolation of this study to other groups of infants must be done with the understanding that population differences could exist and may limit the generalization of results. In addition, interpretation of results for infants less than or equal to 1 kg should be done cautiously. The magnitude of outcome effects for these lowest birth weight infants must be evaluated in reference to the relative smaller number of patients randomized to these weight categories.

SUMMARY

Although the current standard of care for treatment of RDS, exogenous surfactant and CV, has improved pulmonary management for neonates compared with a decade ago, the ability to further reduce ventilator-associated premature lung injury with an HFOV strategy such as the one used in this study lends hope that additional in-roads into the normalization of extrauterine lung development are possible and that further improvements in benign pulmonary support for RDS can be achieved. This study demonstrates that early use of HFOV after surfactant replacement, in combination with a lung recruitment strategy, results in clinical improvement and hospital outcome consistent with reductions in both acute and chronic lung injury. Benefit was evident for preterm infants both less than or equal to 1 kg and more than 1 kg. In addition, initial HFOV treatment appeared to have a more global effect on patient health that lasted throughout the hospitalization, resulting in reduced morbidity and decreased cost of care.

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FUN ON TV

Real life is filled with serial killers, mass murderers, and sickos of all degrees. Much of the twentieth century, it could be argued, has been devoted to the ingenious production and disposal of human corpses. But the scary thing is not that eye-gougings and vivisections and meals of human flesh may occasionally happen. The scary thing, the thing that ought to make the heart pound and the skin go cold and tingly, is that somehow we find this fun to watch on the small and large screens.

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Submitted by Student

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